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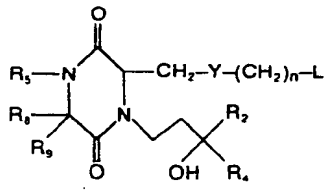
(54) Cyclic diamides, a process for their preparation and their pharmaceutical compositions.

(57) Compounds of the formula (I):



characterised in that

n is 1 to 5;

L is CO_2R wherein R is hydrogen or CO_2R is an ester group in which R contains from 1 to 12 carbon atoms, or CH_2COR_1 wherein R_1 is C_{1-4} alkyl;

Y is $-CH_2CH_2-$, $-CH=CH-$ or $-C\equiv C-$;

R_2 is hydrogen or C_{1-4} alkyl;

R_4 is hydrogen or C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl; or

R_2 and R_4 taken with the carbon atom to which they are joined represent a C_{5-6} cycloalkyl group;

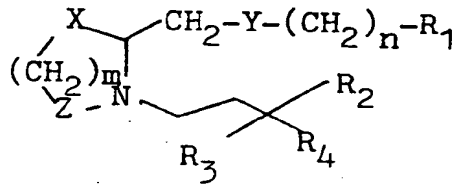
R_5 is NR_6R_7, wherein R_6 and R_7 independently are hydrogen, C_{1-4} alkyl, phenyl C_{1-4} alkyl or NR_6R_7 is a 3 to 7 membered heterocyclic group containing only one hetero atom; hydrogen, C_{1-4} alkyl or C_{1-4} alkyl substituted by an OH, C_{1-4} alkoxy, CN, halogen or NR_6R_7 group as defined above, or by one or two CO_2A groups in which A is hydrogen or a group containing from 1 to 12 carbon atoms; and R_8 and R_9 independently are hydrogen, C_{1-4} alkyl or together with the carbon atom to which they are joined are a C_{3-6} cycloalkyl group; and salts thereof, having activities similar to but more selective than those of natural prostaglandins, a process for their preparation and pharmaceutical compositions containing them.

EP 0 008 186 A1

Cyclic Diamides

This invention relates to novel compounds having pharmacological activity, to a process for their preparation, to intermediates useful in that process and to pharmaceutical compositions containing them.

German Offenlegungsschrift No. 2552312 discloses that compounds of the formula (I)":

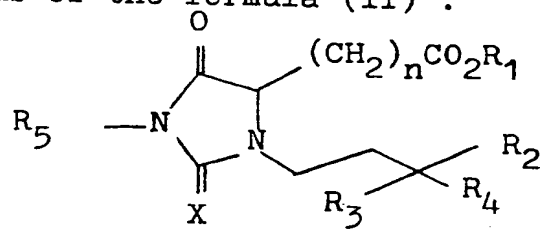


(I)"

wherein:

X is CO, protected CO, CROH in which R is hydrogen or C_{1-4} alkyl and in which the OH moiety may be protected; Y is CH_2CH_2 or CH=CH; Z is CO or CH_2; n is 1 to 8; m is 1, 2 or 3; R_1 is hydrogen, CH_2OH, CH_2OH in which the OH moiety is protected, CO_2W wherein W is hydrogen or CO_2W represents an ester group in which the ester moiety contains from 1 to 12 carbon atoms, or $CONH_2$; R_2 is hydrogen, C_{1-4} alkyl, or taken together with R_3 and the carbon atom to which it is attached represents a carbonyl group; R_3 is hydrogen, hydroxy or protected hydroxy; R_4 is hydrogen or C_{1-9} alkyl; and salts thereof; have useful pharmacological activity.

German Offenlegungsschrift No. 2755711 discloses that compounds of the formula (II)":



(II)"

wherein:

X is O or S;

n is 1 to 8;

R_1 is hydrogen, or CO_2R_1 represents an ester group in which the R_1 moiety contains from 1-12 carbon atoms;

R_2 is hydrogen, C_{1-4} alkyl, or phenyl;

R_3 is hydroxy or protected hydroxy;

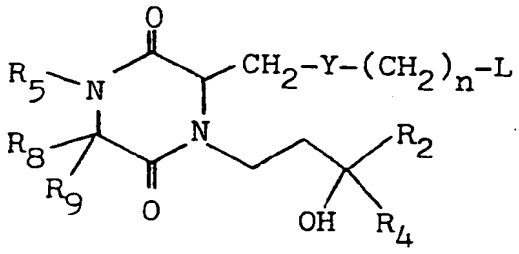
R_4 is hydrogen, C_{1-9} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-6} alkyl, phenyl, phenyl-C_{1-6} alkyl, naphthyl,naphthyl-C_{1-6}-alkyl, any of which phenyl or naphthyl moieties may be substituted by one or more halogen, trifluoromethyl, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, phenyl C_{1-6} alkoxy or nitro groups; or

R_2 and R_4 taken with the carbon atom to which they are joined represent a C_{5-8} cycloalkyl group;

R_5 is hydrogen, C_{1-6} alkyl, C_{1-6} alkyl substituted by a nitro, hydroxy, C_{1-6} alkoxy, CO_2A, $(CO_2A)_2$, CN or halogen group, C_{5-8} cycloalkyl, phenyl, phenyl-C_{1-6} alkyl, phenyl-C_{3-6} cycloalkyl, any of which phenyl moieties may be substituted by one or more halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy or nitro groups; or a group CO_2A; in R_5 when present A is hydrogen or CO_2A represents an ester group in which the A moiety contains from 1 to 12 carbon atoms; and salts thereof; have similarly useful pharmacological activity.

A novel class of compounds also having useful pharmacological activity has now been discovered, which compounds are structurally distinct from the prior art referred to above.

Accordingly, the present invention provides a compound of the formula (I):



(I)

wherein:

n is 1 to 5;

L is CO_2R wherein R is hydrogen or CO_2R is an ester group in which R contains from 1 to 12 carbon atoms; or CH_2COR_1 wherein R_1 is C_{1-4} alkyl;

Y is $-CH_2CH_2-$, $-CH=CH-$ or $-C\equiv C-$;

R_2 is hydrogen or C_{1-4} alkyl;

R_4 is hydrogen or C_{1-9} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-6} alkyl; or

R_2 and R_4 taken with the carbon atom to which they are joined represent a C_{5-8} cycloalkyl group;

R_5 is NR_6R_7 wherein R_6 and R_7 independently are hydrogen, C_{1-4} alkyl, phenyl-C_{1-4} alkyl or NR_6R_7 is a 3 to 7 membered heterocyclic group containing only one hetero atom; hydrogen, C_{1-4} alkyl or C_{1-4} alkyl substituted by an OH, C_{1-4} alkoxy, CN, halogen or NR_6R_7 group as defined above, or by one or two CO_2A groups in which A is hydrogen or a group containing from 1 to 12 carbon atoms; and

R_8 and R_9 independently are hydrogen, C_{1-4} alkyl or together with the carbon atom to which they are joined are a C_{3-6} cycloalkyl group;

and salts thereof.

n is preferably 3.

When L is CO_2R, R is hydrogen or CO_2R is an ester

group in which R contains from 1 to 12 carbon atoms. Examples of R include hydrogen, methyl, ethyl, n- and iso-propyl, n-, sec- and tert-butyl, phenyl, benzyl, tolyl and the like, whilst normally hydrogen or C_{1-6} alkyl groups are preferred.

When L is CH_2COR_1, R_1 is C_{1-4} alkyl. Examples of R_1 include methyl, ethyl, n- and iso-propyl and n-, sec- and tert-butyl, preferably methyl and ethyl, in particular methyl.

Suitable examples of R_2 include hydrogen, methyl and ethyl, preferably methyl.

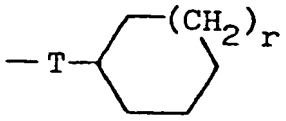
Suitable groups R_4 when R_4 is a C_{1-9} alkyl group include C_{4-9} alkyl groups. Such C_{4-9} alkyl groups may be straight chain alkyl groups, such n-butyl, n-pentyl, n-hexyl and n-heptyl, or may be alkyl groups branched by one or two methyl groups (at the same or different carbon atoms). Thus for example, R_4 may be a group CH_2 M $CH(CH_3)M$ or $C(CH_3)_2$ M wherein M is a straight chain alkyl group such that the carbon content of the resultant group R_4 is 4 to 9.

In general preferred groups R_4 when R_4 is a C_{4-9} alkyl group include straight chain pentyl, hexyl and heptyl groups. Of these, straight chain hexyl is often the most useful. Other preferred groups R_4 include groups $CH(CH_3)M$ and $C(CH_3)_2$ M wherein M is straight chain butyl, pentyl and hexyl.

Other suitable examples of R_4 when R_4 is an alkyl group include the lower alkyl groups, that is when R_4 is a C_{1-4} alkyl group.

When R_4 is or contains a C_{3-8}cycloalkyl moiety, the moiety may be cyclopropyl. The moiety is preferably a C_{5-8} cycloalkyl moiety such as a cyclohexyl moiety.

When R_4 is thus preferably C_{5-8} cycloalkyl or C_{5-8} cycloalkyl-C_{1-6}alkyl, it may be represented by a group of formula (II):



(II)

wherein r is 0 to 3; and

T is a bond or C_{1-6} alkylene.

r is suitably 1.

When T is C_{1-6} alkylene it may be straight-chain or branched. If branched it is preferably branched by one or two methyl groups at the same or different carbon atoms.

Examples of suitable T when C_{1-6} alkylene are groups derived from substitution of the corresponding C_{1-6} alkyl group and include those derived from methyl, ethyl, propyl, butyl and pentyl.

Often T is a group $-(CH_2)_q-$ wherein q is 0 to 4.

Also R_2 and R_4 taken with the carbon atom to which they are joined can represent a C_{5-8} cycloalkyl group, such as a cyclohexyl group.

When R_5 is or contains an acyclic group NR_6R_7, R_6 and R_7 are suitably the same, and may advantageously be hydrogen. However, other suitable examples of such NR_6R_7 include those wherein one or both of R_6 and R_7 are methyl, ethyl and n- and iso-propyl and benzyl.

When R_5 is or contains a heterocyclic group NR_6R_7, suitable examples of such NR_6R_7 include the ring  .

When NR_6R_7 is a heterocyclic group, R_5 is more suitably C_{1-4} alkyl substituted by NR_6R_7, preferably $CH_2NR_6R_7$.

R_5 may also be hydrogen or C_{1-4} alkyl. When R_5 is C_{1-4} alkyl suitable examples of R_5 include methyl, ethyl, n- and iso-propyl, n-, sec- and tert-butyl, more suitably methyl or ethyl, preferably methyl.

R_5 may also be a C_{1-4} alkyl group substituted by an OH, C_{1-4} alkoxy, CN, halogen or NR_6R_7 group as defined, or by one or two CO_2A in which A is a group containing from 1 to 12 carbon atoms.

In such cases R_5 will often be a methyl group so substituted.

Suitable examples of C_{1-4} alkoxy in R_5 include methoxy.

When R_5 contains a group CO_2A, suitable examples of A include hydrogen, methyl, ethyl, n- and iso-propyl, n-, sec- and tert-butyl, phenyl, benzyl, tolyl and the like, whilst normally hydrogen or C_{1-6} alkyl are preferred.

When R_8 and R_9 are hydrogen or C_{1-4} alkyl, they are suitably the same, and may advantageously be hydrogen.

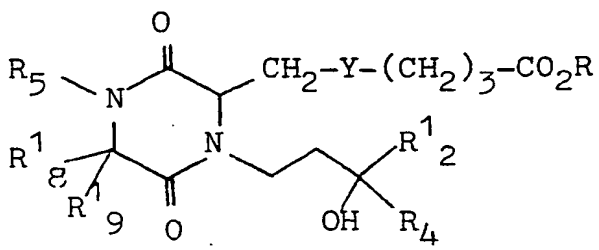
When one or both R_8 and R_9 are C_{1-4} alkyl, suitable examples are methyl, ethyl, n- and iso-propyl and n-butyl, more suitably methyl or ethyl.

R_8 and R_9 taken with the carbon atom to which they are joined can also represent a C_{3-6} cycloalkyl group, such as a cyclopropyl group.

The compounds of the formula (I) may form conventional salts. Such salts include those with alkali and alkaline earth metals, suitably the alkali metals, more suitably sodium or potassium, and also include ammonium and substituted ammonium salts, and acid addition salts when R_5 is or contains NR_6R_7.

The group L when it is CO_2H may be salified. Salts with the alkali metals may also be formed by the displacement of R_5 when hydrogen by an alkali metal atom.

From the aforesaid it will be seen that one particularly suitable group of compounds within formula (I) consists of those of formula (III):



(III)

wherein:

Y, R, R_4 and R_5 are as defined in formula (I);

R^1_2 is hydrogen, methyl or ethyl;

R^1_8 and R^1_9 are the same and are hydrogen, C_{1-4} alkyl or together with the carbon atom to which they are joined are a C_{3-6} cycloalkyl group;

and salts thereof.

Examples of R and preferred R are as so described under formula (I).

R^1_2 is more suitably hydrogen or methyl, preferably methyl.

In formula (III) when R_4 is a C_{1-9} alkyl group it is normally a C_{4-9} alkyl group. Preferred groups R_4 when R_4 is a C_{4-9} alkyl group are as so described under formula (I).

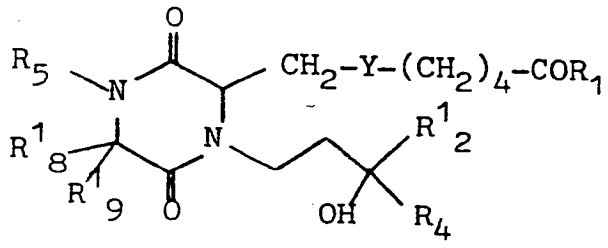
When R_4 is or contains a C_{3-8} cycloalkyl moiety, the moiety is preferably C_{5-8} cycloalkyl, so that preferred R_4 is of formula (II) in this case.

Suitable and preferred R_4 of formula (II) are as so described under formula (II).

Similarly, suitable and preferred R_5 are as so described under formula (I).

Suitable and preferred R^1_8, R^1_9 are as so described for R_8, R_9 under formula (I).

Another particularly suitable group of compounds within formula (I) consists of those of formula (IV):



(IV)

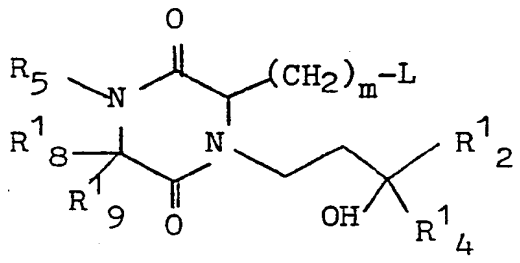
wherein:

R_1 is C_{1-4} alkyl and the remaining variables are as defined in formula (III), and salts thereof.

In formula (IV) examples of R_1 and preferred R_1 are as so described under formula (I).

Examples of the remaining variable groups in formula (IV) and suitable and preferred of these variable groups are as so described under formula (III).

An interesting group of compounds within formula (I) consists of those of formula (V) and salts thereof:



(V)

wherein:

m is 5, 6, 7 or 8;

R_4^1 is hydrogen or C_{1-9} alkyl;

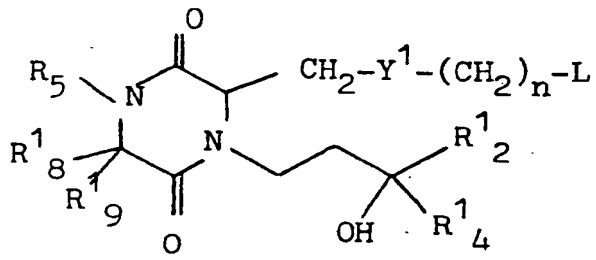
L and R_5 are as defined in formula (I); and the remaining variables are as defined in formula (III).

In formula (V) m is preferably 6.

Whilst R^1_4 may be hydrogen or a C_{1-9} alkyl, it is normally a C_{4-9} alkyl group. In such cases, suitable and preferred groups R^1_4 include those previously so described for the group R_4 when R_4 is a C_{4-9} alkyl group. Of these, straight chain hexyl is often the most useful. Other preferred groups R^1_4 include $CH(CH_3)$ M and $C(CH_3)_2$ M wherein M is straight-chain butyl, pentyl or hexyl.

Examples of the remaining variable groups in formula (V) and suitable and preferred of these variable groups are as so described under formula (III).

Another interesting group of compounds within formula (I) consists of those of formula (VI):



(VI)

wherein:

Y^1 is -CH=CH- or -C≡C-;

n, L and R_5 are as defined in formula (I);

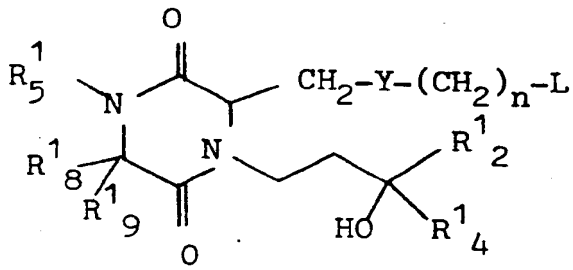
R^1_4 is as defined in formula (V), and the remaining variables are as defined in formula (III); and salts thereof.

In formula (VI) n is preferably 3.

R^1_4 is normally a C_{4-9} alkyl group. Suitable and preferred C_{4-9} alkyl groups R^1_4 are as so described under formula (V). In formula (VI) straight-chain hexyl is again often the most useful.

Examples of the remaining variable groups in formula (VI), and suitable and preferred of these variable groups, are as so described under formula (III).

A further interesting group of compounds within formula (I) consists of those of formula (VII):



(VII)

wherein R_5^1 is hydrogen or C_{1-4} alkyl, and the remaining variables are as defined in formula (III); and salts thereof.

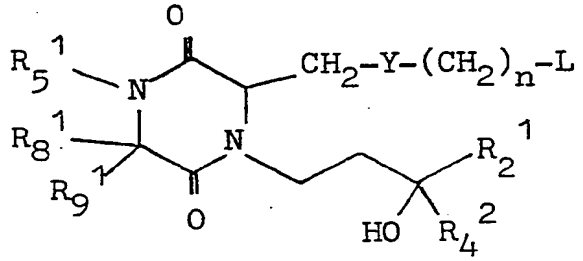
R^1_5 is suitably hydrogen, methyl or ethyl, preferably hydrogen or methyl.

In formula (VII) n is preferably 3.

R^1_4 is normally a C_{4-9} alkyl group. Suitable and preferred C_{4-9} alkyl groups R^1_4 are as so described under formula (V). In formula (VII) straight chain hexyl is again often the most useful.

Examples of the remaining variable groups in formula (VII) and suitable and preferred of these variable groups are as so described under formula (III).

A preferred group of compounds within formula (I) is those of formula (XI):



(XI)

wherein R^2_4 is C_{3-8} cycloalkyl, or C_{3-8} cycloalkyl C_{1-6} alkyl and the remaining variables are as defined in formula (VII), and salts thereof.

R_4^2 is preferably C_{5-8} cycloalkyl, in particular cyclohexyl.

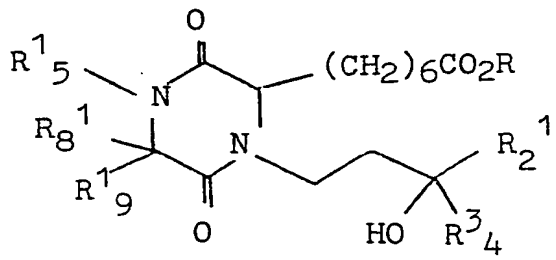
n is preferably 3.

L is preferably a group CO_2R as defined in formula (I).

Y is preferably $-CH_2CH_2-$.

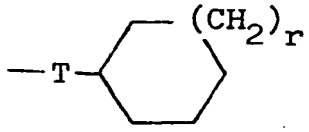
Suitable and preferred remaining variable groups are as so described under formula (III).

A preferred group of compounds within those of formula (XI) are of formula (XII):



(XII)

wherein R_4^3 is a group of formula (II):



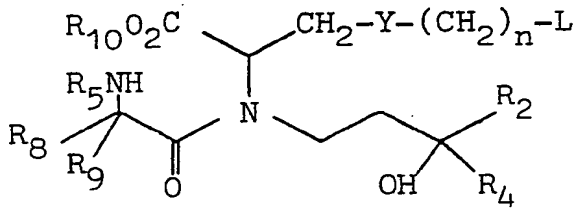
wherein r is 0 to 3; and T is a bond or C_{1-6} alkylene; and the remaining variables are as defined in formula (XI), and salts thereof.

R^2_4 is preferably cyclohexyl.

R^1_5 is preferably methyl.

Other suitable and preferred variable groups are as so described under formula (III).

This invention also provides a process for the preparation of compounds of the formula (I), which process comprises cyclising a compound of formula (VIII):



(VIII)

wherein:

R_{10} is hydrogen or CO_2R_{10} is an ester group in which R_{10} contains from 1 to 12 carbon atoms; and the remaining variables are as previously defined; with elimination of $R_{10}OH$; and thereafter as desired converting R, R_5, R_6, R_7 and/or Y in the compound of formula (I) thus formed into other R, R_5, R_6, R_7 or Y.

The cyclisation is generally effected by warming, for instance . in an inert solvent such as benzene. It should be noted that, when R_5 is a sterically hindering group, the reaction may require effecting with a strong base in a dry organic solvent, such as sodium hydride or sodium ethoxide in benzene or potassium t-butoxide in toluene, benzene or hexamethylphosphoramide.

In general it is convenient in this reaction that when L is CO_2R as defined above, this group is an ester group as defined.

Often it is convenient if R and R_{10} are the same.

The conversion of a compound of the formula (I) wherein CO_2R is an ester group to one wherein R is hydrogen may be achieved by conventional de-esterification. Similarly, compounds wherein R is hydrogen may be esterified conventionally.

When L is a group CO_2H in a compound of the formula (I), salts of the compound at that carboxyl group may be formed conventionally, for example by reacting the compound

with a relevant base.

In general it is convenient that R_5 is hydrogen in the compounds of formula (VIII) and R_5 in corresponding compounds of the formula (I) is converted to different R_5 by conventional substitution.

However, in the compounds of formula (VIII) R_5 may also conveniently be C_{1-4} alkyl.

When R_5 = hydrogen in compounds of formula (VIII) is converted to other R_5 by conventional substitution, this may be carried out by reaction with R_5Q wherein Q is a readily displaceable good leaving group. In such cases, it may often be necessary to convert the compound of the formula (I) wherein R_5 is hydrogen to an alkali metal salt at the lactam group bearing R_5, for example by reacting the compound with a relevant base in a suitable solvent. The base should be a strong base such as sodium in an alcohol such as ethanol, sodium hydride in dimethylformamide or lithium di-isopropylamide in hexamethylphosphoramide.

Suitable examples of Q will be well-known to the skilled man and include for example halides, such as bromide, when R_5 is C_{1-4} alkyl or substituted C_{1-4} alkyl as defined; or substituted aryloxy, such as 2,4-dinitrophenoxy, when R_5 is NR_6R_7 as defined.

The skilled man will realise that substituting an R_5 hydrogen sometimes also substitutes an R hydrogen.

Thus, if it is desired to form a compound of the formula (I) wherein R is hydrogen and R_5 is not by substitution of a compound of the formula (I) wherein R_5 is hydrogen, then it is preferable that CO_2R is initially an ester group which is de-esterified conventionally after the substitution of R_5 hydrogen.

When R_5 is NR_6R_7 or C_{1-4} alkyl substituted by NR_6R_7, the skilled man will realise that, if a compound of the formula (I) is desired wherein R_6 and R_7 are both hydrogen,

then it is frequently desirable to protect the amino group so defined during reaction by means of conventional amine protecting groups R_6 and R_7, such as benzyl groups. Such groups are readily removable by conventional methods such as hydrogenolysis.

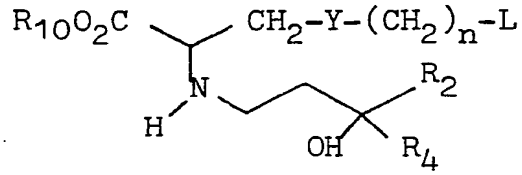
Similarly, groups NR_6R_7 wherein R_6 and R_7 are hydrogen may be alkylated or aralkylated conventionally.

When R_5 is or contains a group NR_6R_7 in a compound of the formula (I), acid addition salts of the compound at that group may be formed conventionally, for example by reacting the compound with a relevant acid.

Compounds wherein Y is -C≡C- may be reduced to compounds wherein Y is -CH=CH- in known manner, suitably by catalytic hydrogenation, for example using Lindlar catalysis.

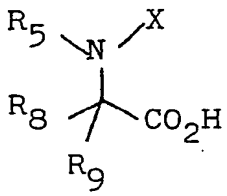
Similarly when Y is -CH=CH-, it may be reduced to $-CH_2CH_2-$ in known manner, suitably by catalytic hydrogenation, for example, using transition metals.

The compounds of formula (VIII) may be prepared by reacting a compound of formula (IX):



(IX)

wherein the variables are as previously defined, with a compound of formula (X):



(X)

wherein:

X is a conventional amine protecting group; and the remaining variables are as previously defined; or with

such a compound containing a reactive derivative of the CO_2H group thereof; and thereafter replacing X conventionally by a hydrogen atom.

Conventional amine protecting groups are those which are readily removeable by conventional mild methods such as mild hydrolysis or hydrogenolysis. Examples of such groups include benzyloxycarbonyl.

Suitable reactive derivatives of the CO_2H group include the corresponding halides or anhydrides.

Where the free acid (X) is used the reaction is preferably carried out in the presence of a condensation promoting dehydrating agent such as dicyclohexylcarbodiimide.

X is suitably removed from the compound so formed by mild hydrogenolysis, for example using hydrogen in the presence of a transition metal catalyst such as palladium on charcoal.

The compound of the formula (VIII) is often conveniently formed <u>in situ</u> by the above process, and cyclised directly to the corresponding compound of the formula (I) without isolation.

It is believed that the compounds of formula (VIII) are novel, and thus form an important aspect of this invention as intermediates.

The compounds of formula (IX) may be prepared by the method disclosed in German Offenlegungsschrift Nos: 2552312, 2647969 and 2724948 and our co-pending European Application No. 79301145.3.

The compounds of the formula (I) have asymmetric centres, and can thus exist in several sterisomeric forms. The invention extends to each of these forms, and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated mutually by usual methods

Isomers having a common stereospecific feature may be obtained by stereospecific synthesis. Isomers having a common chiral centre may be obtained by asymmetric synthesis, e.g. from chiral intermediates.

Compounds of the formula (I) have useful pharmacological activity. For example compounds of the formula (I) have anti-gastric secretion activity e.g. anti-ulcer activity, cardiovascular activity e.g. anti-hypertensive activity, platelet aggregation inhibition activity, affect the respiratory tract e.g. bronchodilator activity, anti-fertility activity, smooth muscle activity and/or anti-arrhythmic activity.

In general it may be said that compound within the formula (I) have a range or pharmacological activities similar to those shown by the natural prostaglandins, but that their activity profiles tend to be rather more selective so that each compound tends to have a major activity readily ascertained by routine pharmacological tests. By way of example, it has been found that many of the compounds fo the formula (I) are especially useful as bronchodilator agents, such as in particular compounds of the fomulae (V) and (XI).

The invention therefore also provides a pharmaceutical composition comprising a compound of the formula (I) and a pharmaceutically acceptable carrier.

In order to utilise the selectivity of activity found with compounds of the formula (I), normally a given compound will be used in the treatment of the disorder corresponding to the compound's major activity (that is, the disorder for which the compound has the lowest active dose) and will accordingly be formulated into the corresponding pharmaceutical composition, and administered in a manner conventional for treatment of that disorder. It may also of course be possible with compounds having one or more further pronounced activities to formulate and use the compound for those further activities as well as for the major activity, provided that there is no undesirable pharmacological interaction between the different activities, or that separation of the different activities can be obtained by a difference in the formulation or in the mode of administration.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, fillers, tabletting lubricants, disintergrants, and acceptable wetting agents and the like. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and if desired conventional flavouring or colouring agents, and the like.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound of the formula (I) and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents can be dissolved in the vehicle. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by

filtration. The compound can be sterilized by exposure to ethylene oxide before suspensing in the sterile vehicle. Advantageously, a sufactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

When appropriate, the compositions of this invention may be presented as an aerosol for oral administration, or as a microfine powder for insufflation.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

It will of course be realised that the precise dosage used in the treatment of any of the hereinbefore described disorders will depend on the actual compound of the formula (I) used, and also on other factors such as the seriousness of the disorder being treated.

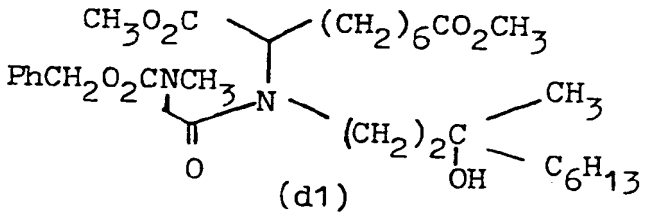
The invention also provides a method of treatment and/or prophylaxis of disorders in human beings or domestic animals which comprises the administration to the sufferer of an effective amount of a compound of the formula (I).

The following Example illustrates the preparation of compounds of the formula (I).

The following Description illustrates the preparation of intermediates for the compounds of the formula (I).

DESCRIPTION

Dimethyl 2-[N-(3'-hydroxy-3'-methylnonyl)-N-{2"-(N'-methyl-N'-benzyloxycarbonylamino)acetyl}amino]azelate.



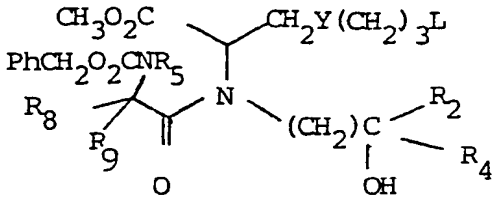
(d1)

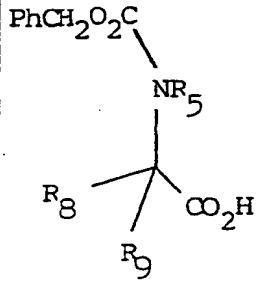
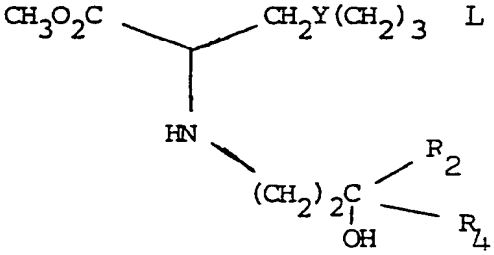
Dicyclohexyl carbodiimide (10.65g) in dichloromethane (50ml) was added dropwise, under nitrogen, at room temperature, to a stirred mixture of N-benzyloxycarbonyl sarcosine (11.53g) and dimethyl 2-[N-(3'-hydroxy-3'-methyl)nonyl]aminoazelate (20g) in dichloromethane (200ml). The mixture was stirred at room temperature overnight then was filtered through kieselguhr. The filtrate was chromatographed on silica gel (600g) using chloroform as eluent. Dimethyl 2-[N-(3'-hydroxy-3'-methylnonyl)-N-{2"-(N'-methyl-N'-benzyloxycarbonyl-amino) acetyl}amino] azelate (19.5g) was obtained as a colourless gum

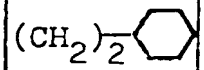
I.r: ν_{max} (film) cm^{-1} 3450, 1740, 1710, 1660.

The compounds shown in Table 1 were produced in a similar way, using the appropriate intermediates (A and B).

Table 1

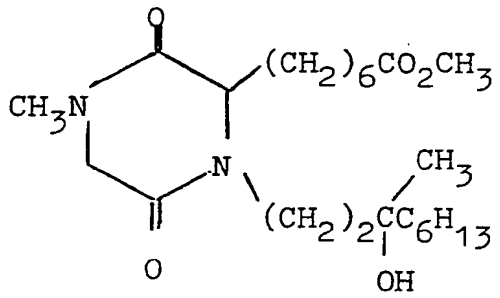


COMPOUND	Intermediate A			Intermediate B			
							
	R_5	R_8	R_9	R_2	R_4	Y	L
d2	H	H	H	CH_3	C_6H_{13}	CH_2CH_2	CO_2CH_3
d3	CH_3	H	H	CH_3	$CH(CH_3)C_4H_9$	CH_2CH_2	CO_2CH_3
d4	CH_3	H	H	CH_3	C_2H_5	CH_2CH_2	CO_2CH_3
d5	CH_3	H	H	CH_3		CH_2CH_2	CO_2CH_3
d6	H	H	H	CH_3		CH_2CH_2	CO_2CH_3

	R_5	R_8	R_9	R_2	R_4	Y	L
d 7	H	H	H	H	C_2H_5	CH_2CH_2	CO_2CH_3
d 8	H	H	H			CH_2CH_2	CO_2CH_3
d 9	CH_3	H	H	CH_3		CH_2CH_2	CO_2CH_3
d 10	H	CH_3	H (L-isomer)	CH_3		CH_2CH_2	CO_2CH_3
d 11	CH_3	H	H	CH_3	C_6H_{13}	CH_2CH_2	CH_2COCH_3

EXAMPLE 1

1-(3'-hydroxy-3'-methylnonyl)-4-methyl-6-(6"-methoxycarbonylhexyl) piperazine-2,5-dione.



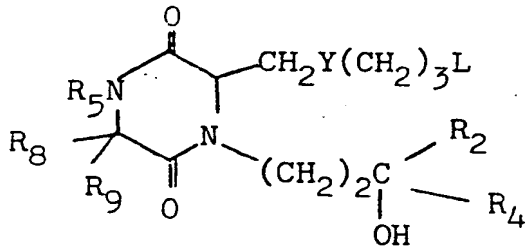
(f)

Dimethyl 2-[N-(3'-hydroxy-3'-methylnonyl)-N-{2"-(N-methyl-N'-benzyloxycarbonylamino)acetyl}amino]azelate (15g) was hydrogenolysed, at atmospheric pressure and room temperature, over 10% palladium on charcoal (3g) in dimethoxyethane (300ml). When hydrogen uptake was completed, the mixture was filtered through kieselguhr and the filtrate was evaporated in vacuo to give a clear gum (9.5g). This was purified via column chromatography on silica gel (100g) using chloroform as eluant to give 1-(3'-hydroxy-3'-methylnonyl)-4-methyl-6-(6"-methoxycarbonylhexyl)-piperazine-2,5-dione (7.6g) as a colourless gum.

I.r. ν_{max} (film) cm^{-1} 3450, 1740, 1660 (broad)

The compounds shown in Table 2 were prepared in a similar manner.

Table 2



Compound	R_2	R_4	R_5	R_8	R_9	Y	L
2	CH_3	C_6H_{13}	H	H	H	CH_2CH_2	CO_2CH_3
3	CH_3	$CH(CH_3)C_4H_9$	CH_3	H	H	CH_2CH_2	CO_2CH_3
4	CH_3		CH_3	H	H	CH_2CH_2	CO_2CH_3
5	CH_3		H	H	H	CH_2CH_2	CO_2CH_3

Table 2 (continued)

Compound	R_2	R_4	R_5	R_8	R_9	Y	L
6	H	C_2H_5	H	H	H	CH_2CH_2	CO_2CH_3
7			H	H	H	CH_2CH_2	CO_2CH_3
8	CH_3	$(CH_2)_2$- 	CH_3	H	H	CH_2CH_2	CO_2CH_3
9	CH_3		H	CH_3	H	CH_2CH_2	CO_2CH_3
14	CH_3	C_6H_{13}	CH_3	H	H	CH_2CH_2	CH_2COCH_3

Characterising Data

Compound 4

Analysis: $C_{23}H_{40}N_2O_5$ requires: C, 65.06; H, 9.50; N, 6.60%

found: C, 65.11; H, 9.18; N, 6.44%

I.r. ($CHCl_3$)cm^{-1}: 3450, (OH); 1735, (CO_2CH_3); 1660 (CON<).

N.m.r.: ($CDCl_3$)τ: 7.8 (bs, 1H, OH);
7.7 (m, 2H, $C\underline{H}_2CO_2CH_3$);
7.05 (s, 3H, NCH_3);
6.35 (s, 3H, CO_2CH_3);
6.2 to 5.8 (m, 3H, $COCH_2N$; NCH).

Mass spectrum: $C_{23}H_{40}N_2O_5$ (m*) requires: 424.2935
found: 424.2956

Compound 5

Analysis: $C_{22}H_{38}N_2O_5$ requires C, 64.36; H, 9.33; N, 6.82%
found: C, 64.57; H, 9.56; N, 6.45%

I.r. (υ max) ($CHCl_3$) cm^{-1}: 3450 to 3200, (OH; NH); 1735, (CO_2CH_3); 1680 and 1645 (CONH and CON$\prec$).

Mass spectrum: $C_{22}H_{38}N_2O_5$ (m*) requires: 410.2778
found: 410.2787

Compound 6

Analysis: $C_{17}H_{30}N_2O_5$ requires: C, 59.63; H, 8.83; N, 8.18%
found: C, 59.13; H, 8.70; N, 7.95%

N.m.r ($CDCl_3$)τ: 7.65 (t, 2H, $C\underline{H}_2CO_2CH_3$);
6.4 (centre of brm, 5H, CHOH, NCH_2, NCH);
6.3 (s, 3H, CO_2CH_3);
5.95 (bs, 2H, NCH_2CON);
2.65 (bs, 1H, CONH).

Mass spectrum $C_{17}H_{30}N_2O_5$ (m*) requires: 342.2155
found: 342.2157

Compound 7

Analysis: $C_{20}H_{34}N_2O_5$ requires: C, 62.80; H, 8.96; N, 7.32%
found: C, 62.69; H, 9.09; N, 7.29%

N.m.r. ($CDCl_3$)τ: 7.7 (t, 2H, $C\underline{H}_2CO_2CH_3$);
7.45 (s, 1H, OH);
6.85 (bm, 2H, NCH_2);
6.35 (s, 3H, CO_2CH_3);
6.05 (b, 3H, NCH_2CON; NCH);
2.6 (bs, 1H, CONH).

Mass spectrum: $C_{20}H_{34}N_2O_5$ (m*) requires: 382.2468
found: 382.2468

Compound 8

N.m.r. ($CDCl_3$) τ: 7.75 (t, 2H, $C\underline{H}_2CO_2CH_3$);
7.72 (s, 1H, OH);
6.9 (centre of br m, 2H, NCH_2);
7.05 (s, 3H, NCH_3);
6.35 (s, 3H, CO_2CH_3);
6.1 (d, 2H, NCH_2CON);
5.95 (m, 1H, NCH).

Compound 9

I.r. (νmax) ($CHCl_3$) cm^{-1} 3500 - 3200 (OH,NH);
1740, (CO_2CH_3);
1680 (CONH);
1640, (CON=).

N.m.r. ($CDCl_3$) τ: 7.7 (t, 2H, $C\underline{H}_2CO_2CH_3$);
7.4 (bs, 1H, OH);
6.8 (centre of brm, 2H, NCH_2);
6.35 (s, 3H, CO_2CH_3);
6.0 (m, 2H, 2 x COCHN);
2.35 (b, 1H, CONH).

Compound 14

Analysis: $C_{24}H_{44}N_2O_4$ requires: C, 67.89;
H, 10.44; N, 6.60%
found C, 67.97; H, 10.77; N, 6.51

I.r. (max) ($CHCl_3$) cm^{-1}: 3440, (OH)
1720, ($COCH_3$)
1660, br, (CON)

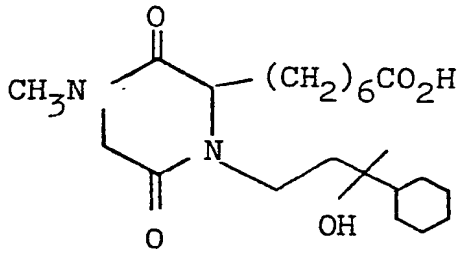
N.m.r. ($CDCl_3$)τ: 7.9 (s, 3H, $COCH_3$);
7.6 (t, 2H, $C\underline{H}_2COCH_3$);
7.5 (s, 1H, OH);
7.0 (s, 3H, NCH_3);

6.6 (centre bm, 2H, $CONCH_2$);
6.05 (m, 3H, ring $-CH_2-$, ring≡CH)

Mass spectrum: $C_{24}H_{44}N_2O_4$ (m*)
requires: 424.3301
found: 424.3317

Example 2

1-(3'-hydroxy-3'-cyclohexylbutyl)-4-methyl-6-(6"-carboxyhexyl)-piperazine-2,5-dione



(10)

1-(3'-hydroxy-3'-cyclohexylbutyl)-4-methyl-6-(6"-methoxycarbonylhexyl)-piperazine-2,5-dione (4) (1.05g, 2.5 mmol) was dissolved in methanol (20ml) and 10% aqueous potassium carbonate (15 ml) was added. The mixture was stirred at room temperature for eighteen hours and partitioned between diethyl ether (3 x 50ml) and water (150 ml). The aqueous phase was acidified with 5M aqueous hydrochloric acid and extracted with diethyl ether (3 x 50 ml). The combined diethyl ether layers were washed with brine until neutral and dried over sodium sulphate. The solvent was removed under reduced pressure, and the yellow gum so obtained was recrystallised using ethyl acetate/hexane as solvent to give 1-(3'-hydroxy-3'-cyclohexylbutyl)-4-methyl-6-(6"-carboxyhexyl)-piperazine-2,5-dione (0.65g, 64%) as a white powder.

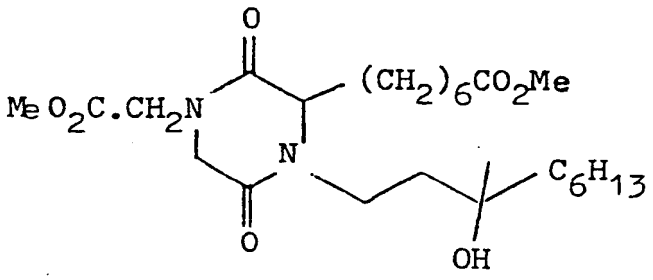
I.r. (ν max) cm^{-1}: 3425 (O-H), 3.50-2500 (CO_2H), 1720 (CO_2HO), 1660 (amide)

N.m.r. ($CDCl_3$)τ : 3.89 (bs, 2H, O-H, CO_2-H exch D_2O); 7.06 (s, 3H, N-CH); 7.70 (2H, t, CH_2-CO_2H)

Analysis: $C_{22}H_{38}N_2O_5$ requires : N, 6.82; C, 64.36; H, 9.33%
found: N, 6.68; C, 64.07; H, 9.47%

Example 3

1-(3'-hydroxy-3'-methylnonyl)-4-methoxycarbonylmethyl-6-(6"-methyoxycarbonylhexyl)-piperazine-2,5-dione



(11)

To a stirred slurry of sodium hydride (0.146g, 4.9 mmole) (80% dispersion in oil) in dry benzene (10ml) under a nitrogen atmosphere was added 1-(3'-hydroxy-3'-methylnonyl)-6-(6"-methoxycarbonylhexyl)-piperazine-2,5-dione (2.0g, 4.9 mmol) in dry dimethylformamide (10ml). After stirring for ten minutes, a clear colourless solution was obtained. Methyl bromoacetate (0.75g, 4.9 mmol) was added dropwise over half a minute. The solution was stirred at room temperature and then heated to reflux. A precipitate soon appeared. After three hours at reflux, the mixture was cooled, diluted with diethyl ether (200 ml) and washed with brine (3 x 40 ml). The solution was dried over sodium sulphate and the solvent was removed under reduced pressure. The oil so obtained was chromatographed on silica gel (30g) using ethyl acetate/hexane (1:1) and then ethyl acetate as eluant to give 1-(3'-hydroxy-3'-methylnonyl)-4-methoxy-carbonylmethyl--6-(6"-methoxycarbonylhexyl-piperazine-2,5-dione (1.25 g, 53%) as a low melting white solid.

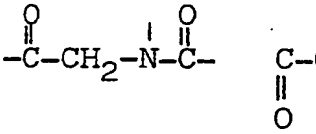
I.r. (cm^{-1}) (ν max): 3425 (O-H), 1740 (ester), 1665 (amide).

N.m.r. ($CDCl_3$)τ: 5.2-6.8 (m, 13H, $MeO_2C.\underline{CH_2}N$-, $-C(=O)-\underline{CH_2}-N-C(=O),C(=O)-CH-N$, $-C(=O)-N-\underline{CH_2}$, 2 x CO_2CH_3); 7.15 (s, 1H, O-H exchange D_2O), 7.70(t, 2H, $CH_2\underline{CH_2}CO_2Me$)

H.r.m.s.: Found 484.3168, $C_{25}H_{44}N_2O_7$ requires 484.3147

1-(3'-hydroxy-3'-cyclohexylbutyl)-4-cyanomethyl-6-(6"-methoxycarbonylhexyl)-piperazine-2,5-dione (12) was similarly prepared from 1-(3'-hydroxy-3'-cyclohexylbutyl)-6-(6"-methoxycarbonylhexyl)-piperazine-2,5-dione and chloroacetonitrile in 45% yield.

I.r. (ν max) cm^{-1} 3450 (O-H), 1735 (ester), 1665 (amide).
N.m.r. ($CDCl_3$) τ: 5.3-6.1 (bm, 5H, $NC-CH_2-N=$

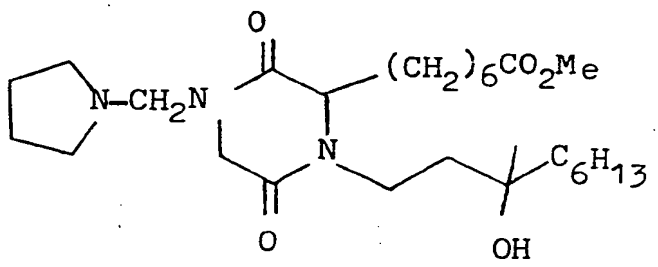


C-CH-N); 6.36, (s, 3H, CO_2CH_3).

H.r.m.s.: Found 431.2784 ($M^+ - H_2O$); $C_{24}H_{37}N_3O_4$ requires 431.2782.

Example 4

1-(3'-hydroxy-3'-methylnonyl)-4-pyrrolidinomethyl-6-(6"-methoxycarbonylhexyl)-piperazine-2,5-dione



(13)

A mixture of 1-(3'-hydroxy-3'-methylnonyl)-6-(6"-methoxycarbonylhexyl)-piperazine-2,5-dione(1.4g, 3.4 mmol), 40% aqueous formaldehyde (0.29 ml 3.9 mmol) and pyrrolidine (0.27g, 3.8 mmol) in ethanol (10ml) was heated to reflux for eighteen hours. The resulting yellow solution was cooled, diluted with diethyl ether (200 ml) and washed with brine (3 x 40 ml). After drying over sodium sulphate, the solvent was removed under reduced pressure, and the dark yellow oil so obtained was chromatographed on neutral alumina (25g) using chloroform as eluent. This gave 1-(3'-hydroxy-3'-methylnonyl)-4-pyrrolidinomethyl-6-(6"-methoxycarbonylhexyl)-piperazine-2,5-dione (1.1g 65%).

I.r. (ν max) cm^{-1}: 3430 (O-H), 1740 (ester), 1660 (amide).

N.m.r. ($CDCl_3$)τ: 5.5 - 6.1 (5H, N-$\underline{CH_2}$-N; $-\overset{O}{\overset{\|}{C}}-CH_2-\overset{|}{N}-\overset{O}{\overset{\|}{C}}-$; $-\overset{O}{\overset{\|}{C}}-\overset{|}{CH}-N$), 6.36 (s, 3H, CO_2CH_3); 7.40 (bm, 4H, 2 x CH_2N).

H.r.m.s.: Found 495.3680, $C_{27}H_{49}N_3O_5$ requires 495.3670

PHARMACOLOGICAL DATA

Bronchodilation Activity

1. The compounds were examined for their ability to inhibit 5-hydroxytryptamine or histamine induced bronchoconstriction in the anaesthetised, artifically respired guinea pig (Konzett-Rossler preparation). The compounds were administered intravenously. The results are shown in Table A.

Table A

Compound number	ED_{50} as defined above (μg/kg i.v.)
1	4.4
3	4.3
4	0.59

2. Compound 3 was also examined for its ability to protect conscious guinea pigs against bronchoconstriction induced by an histamine aerosol (Herxheimer test). In these experiments the compound was administered by aerosol or by oral administration. The results are the mean of several experiments. Compound 3 was active at 10 mg/kg.

Anti-gastric sectory activity

The compounds were examined for their ability to inhibit pentagastrin-stimulated gastric acid secretion in the anaesthetised, perfused rat stomach preparation (Ghosh and Schild preparation). The compounds were administered intravenously.

Compounds 3 and 9 inhibited gastric acid secretion at 0.2 and 0.25 mg/kg, i.v., respectively.

Anti-ulcer activity

Anti-ulcer activity was assessed by the inhibition of indomethacin induced gastric damage in the rat according to the method of Eleghe (1974) Israeli J. Med. Sci. 10 1451. Rats were starved overnight given 15mg/kg indomethacin subcutaneously and sacrificed 4 hours later. Stomachs were reflated with n. saline, cut along the greater curvature pinned out and scored for gastric damage by the following system:

Score 1 - 3 - according to degree of erythema and slight haemorrhage.

Score 4 - 6 - according to degree of mucosal erosion.

Score 7 - 9 - according to depth of gastric damage.

Groups of 7 rats were used for each treatment and the test compound or vehicle were administered 30 minutes prior to giving the indomethacin. Dose of test compound was 50mg/kg orally and control groups receiving vehicle only were set up simultaneously. Mean values for each treatment were obtained using the above scoring system and the Mann Witney test applied for significance of difference between the values obtained with the treatments.

The results are shown in Table B

Table B

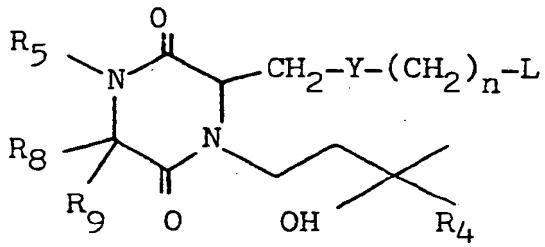
Compound number	Vehicle Mean Score ± S.E. of Mean	Test Mean Score ± S.E. of Mean
3	4.57 ± 0.69	0.71 ± 0.42 ($p < 0.01$)

Toxicity

No toxic effects were observed in any of the above tests.

CLAIMS

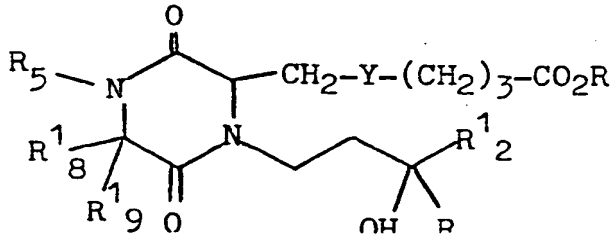
1. A compound of formula (I):



(I)

characterised in that
n is 1 to 5;
L is CO_2R wherein R is hydrogen or CO_2R is an ester group in which R contains from 1 to 12 carbon atoms, or CH_2COR_1 wherein R_1 is C_{1-4} alkyl;
Y is $-CH_2CH_2-$, $-CH=CH-$ or $-C\equiv C-$;
R_2 is hydrogen or C_{1-4} alkyl;
R_4 is hydrogen or C_{1-9} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-6} alkyl; or
R_2 and R_4 taken with the carbon atom to which they are joined represent a C_{5-8} cycloalkyl group;
R_5 is NR_6R_7 wherein R_6 and R_7 independently are hydrogen, C_{1-4} alkyl, phenyl C_{1-4} alkyl or NR_6R_7 is a 3 to 7 membered heterocyclic group containing only one hetero atom; hydrogen, C_{1-4} alkyl or C_{1-4} alkyl substituted by an OH, C_{1-4} alkoxy, CN, halogen or NR_6R_7 group as defined above, or by one or two CO_2A groups in which A is hydrogen or a group containing from 1 to 12 carbon atoms; and R_8 and R_9 independently are hydrogen, C_{1-4} alkyl or together with the carbon atom to which they are joined are a C_{3-6} cycloalkyl group; and salts thereof.

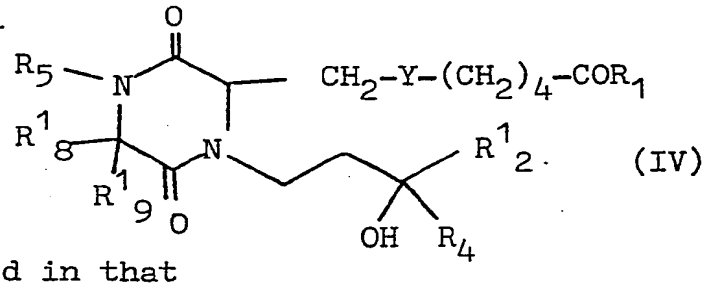
2. A compound according to claim 1 of formula (III):



(III)

characterised in that
Y, R, R_4 and R_5 are as defined in claim 1;
R^1_2 is hydrogen, methyl or ethyl;
R^1_8 and R^1_9 are the same and are hydrogen, C_{1-4} alkyl or together with the carbon atom to which they are joined are a C_{3-6} cycloalkyl group;
and salts thereof.

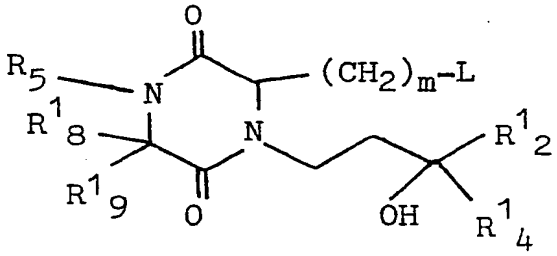
3. A compound according to claim 1 of formula (IV):



(IV)

characterised in that
R_1 is C_{1-4} alkyl and the remaining variables are as defined in claim 2; and salts thereof.

4. A compound according to claim 1 of formula (V) and salts thereof:

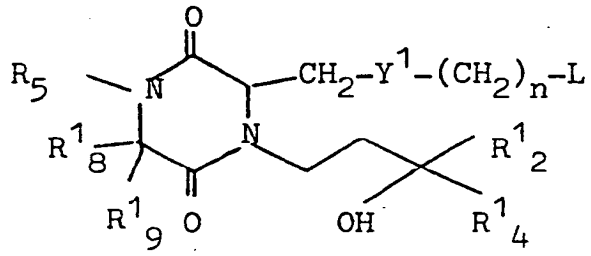


(V)

characterised in that
m is 5, 6, 7 or 8;
R_4^1 is hydrogen or C_{1-9} alkyl;
L and R_5 are as defined in claim 1; and the remaining variables are as defined in claim 2.

5. 1-(3'-hydroxy-3'-methylnonyl)-4-methyl-6-(6"-methoxycarbonylhexyl)piperazine-2,5-dione.

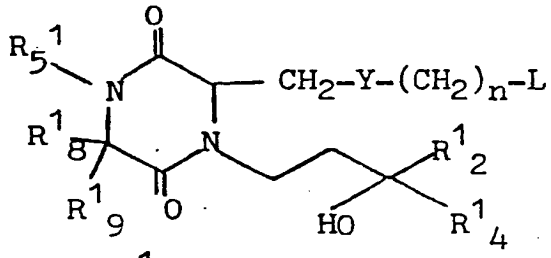
6. A compound according to claim 1 of formula (VI):



(VI)

characterised in that
Y^1 is -CH=CH- or -C≡C-;
n, L and R_5 are as defined in claim 1;
R^1_4 is as defined in claim 4 , and the remaining variables are as defined in claim 2 and salts thereof.

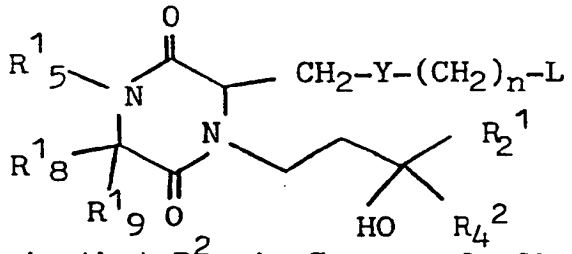
7. A compound according to claim 1 of formula (VII):



(VII)

charaterised in that R_5^1 is hydrogen or C_{1-4} alkyl, and the remaining variables are as defined in claim 4, and salts thereof.

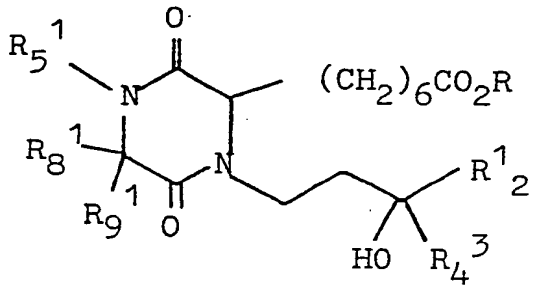
8. A compound according to claim 1 of formula (XI):



(XI)

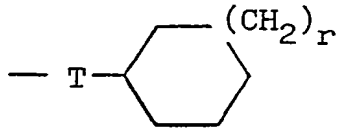
characterised in that R^2_4 is C_{3-8} cycloalkyl, or C_{3-8} cycloalkyl—C_{1-6} alkyl and the remaining variables are as defined in claim 7, and salts thereof.

9. A compound according to claim 8 of formula (XII):



(XII)

characterised in that R^3_4 is a group of formula (II):



(II)

wherein r is 0 to 3; and
T is a bond or C_{1-6} alkylene and the remaining variables are as defined in claim 8, and salts thereof.

10. 1-(3'-hydroxy-3'-cyclohexylbutyl)-4-methyl-6-(6"-methoxycarbonylhexyl)piperazine-2,5-dione.

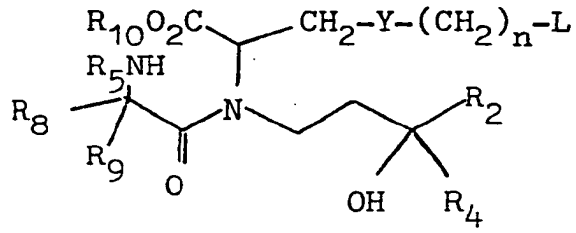
11. 1-(3'-hydroxy-3'-cyclohexylbutyl)-4-methyl-6-(6"-carboxyhexyl)piperazine-2,5-dione.

12. The sodium salt of the compound of claim 11.

13. A pharmaceutical composition comprising a compound according to claim 1 together with a pharmaceutically acceptable carrier.

14. A pharmaceutical composition comprising the compound of any one of claims 10 to 12 together with a pharmaceutically acceptable carrier.

15. A process for the preparation of a compound of formula (I), characterised by cyclising a compound of formula (VIII):

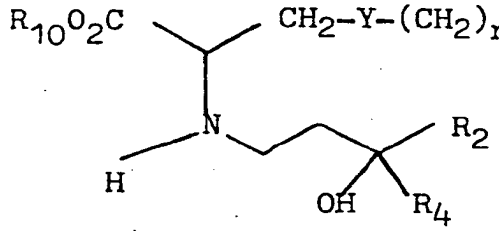


(VIII)

wherein:

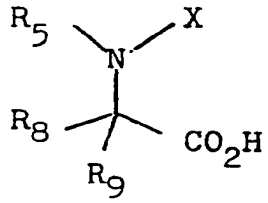
R_{10} is hydrogen or CO_2R_{10} is an ester group in which R_{10} contains from 1 to 12 carbon atoms; and the remaining variables are as previously defined; with elimination of $R_{10}OH$; and thereafter as desired converting R, R_5, R_6, R_7 and/or Y in the compound of formula (I) thus formed into other R, R_5, R_6, R_7 or Y.

16. A process according to claim 13 characterised in that the compound of formula (VIII) is formed <u>in situ</u> by reacting a compound of formula (IX):



(IX)

wherein the variables are as previously defined, with a compound of formula (X):



(X)

wherein:

X is a conventional amine protecting group; and the remaining variables are as previously defined; or with such a compound containing a reactive derivative of the CO_2H group thereof; and therafter replacing X conventionally by a hydrogen atom.

17. 1-(3'-hydroxy-3',4'-dimethyloctyl)-4-methyl-6-(6"-methoxycarbonylhexyl)piperazine-2,5-dione.

European Patent Office

EUROPEAN SEARCH REPORT

0008186
Application number

EP 79 30 1518

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	BE - A - 861 956 (BEECHAM)	

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 241/08
A 61 K 31/495 //
A 61 K 31/557

TECHNICAL FIELDS SEARCHED (Int.Cl.³)

C 07 D 241/08
A 61 K 31/495

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	24-09-1979	BERTE

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